

EFFICACY REVIEW

PRODUCT: SVP7

EPA Reg. No.: 83399-6

DATE: May 29, 2008

DP BARCODE: D352805

GLP: No

CHEMICAL: Permethrin (36.08%)
Dinotefuran (4.95%)
Pyriproxyfen (0.44%)

CHEMICAL NUMBER: Permethrin.....109701
Dinotefuran.....044312
Pyriproxyfen....129032

PURPOSE: Review resubmission- claims for lice, mites, flies and additional marketing claims

MRID: 47316001. Conti. J.A. 2007. Efficacy Support Document; Summit VetPharm, Fort Lee, NJ; Company ID SVP7-1107

TEAM REVIEWER: Rita Kumar

EFFICACY REVIEWER: Joanne S. Edwards, M.S., Entomologist *Joanne S Edwards 5/29/08*

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BACKGROUND:

SVP7 is registered for the control of ticks, fleas, and mosquitoes on dogs and puppies over seven weeks of age. The application rate is: (1.6 ml) 0.06 fl oz for weights 2.5 to 20 lbs., (3.6 ml) 0.12 fl oz for weights 20 to 55 lbs, (4.7 ml) 0.16 fl oz for weights 56 to 95 lbs, and (8 ml) 0.3 fl oz for over 95 pounds. The registrant is requesting to add additional claims for control of lice, mites and flies. See previous efficacy review dated April 11, 2008 under D349709.

DATA REVIEW:

1. Delete all claims referencing West Nile virus.

Registrant Response: West Nile Virus (WNV) continues to be a problem in geographic pockets throughout the United States, although no longer capable of demanding major media coverage in part because of the excellent response by EPA and the pesticide manufacturing community in developing and educating the public on the disease and the required precautions to avoid the disease. The label language offered will continue to keep the public educated and aware of the benefits of mosquito protection. Dogs may not be recognized as host for WNV, but they are still bitten by mosquitoes and can be afflicted with WNV. Considering the large population of dogs in the United States, more than 55 million, and their close association with humans and the concerns by pet owners about vector transmitted diseases, Summit believes that a claim of kills and repels mosquitoes is not easily associated by consumers to translate into protection vs. WNV. Pet owners who camp or maintain their dogs in outside kennels continue to ask questions about WNV. In the documents supplied by the registrant, the Center for Disease Control and the United States Army confirm that mosquitoes can bite and infect unprotected dogs with WNV. Quoting from Dr. Stephen Ostroff CDC, "The more the CDC knows about the mosquito that transmit the virus, the better it can advise the public on how to reduce the infection". In documents which were provided, the CDC does not recommend using human repellants because of possible licking issues but does advise consumers to consult their veterinarian for recommendation. Without the claim as stated veterinarians and the manufacturer cannot legally pass along this type of information; although, the recommendation of the CDC appears to establish the veterinarian as the expert in assisting the pet owner with vector born diseases transmitted by mosquitoes i.e., off label claim for the product. We request that EPA reconsider the claim citing the example that EPA's conclusions do not fall in line with other units in the pesticide division who permit similar but unrelated claims. In the case of antimicrobials, which reduce or eliminate bacterial contamination, there would typically be no clinically detrimental effect to humans if they were contaminated with the bacteria or virus homeowners typically employ them to kill.

Our Response: The Pesticide Efficacy Review Committee (PERC) considered Summit VetPharm's comments, and the conclusions are not altered. This is because there is a lack of cases and no demonstrated clinical symptoms of WNV in dogs. Also, dogs don't pose a risk as alternate hosts.

2. Delete all claims relating to lice.

Company Response: Lice. EPA's review quotes that in the submitted study an unknown number of dogs were treated with permethrin applied at a dosage of 85.7 mg/kg. Using the data on page 63/153, this information was available in the table. To further define the data the registrant offers the following table comparing the permethrin dose given to the study animal vs. the permethrin dose the same dog would receive if treated with SVP7;

<u>Dog weight</u>	<u>Dose Permethrin (study)</u>	<u>SVP7 equivalent</u>
22kg	59.09mg/kg	59.04mg/kg
7 kg	92.8mg/kg	82.44mg/kg
16.9kg	76.9mg/kg	34.0mg/kg
19.5kg	66.66mg/kg	66.44mg/kg
19.4kg	67.0mg/kg	66.95mg/kg
60.2 kg	43.0mg/kg	47.94mg/kg
53.6kg	24.0mg/kg	53.8mg/kg
5.0 kg	130.0mg/kg	115.45mg/kg
20.7kg	62.8mg/kg	62.7mg/kg
4.4kg	147.0mg/kg	131.2mg/kg

Using the above table and calculations understanding that the permethrin component of the formulation is the active ingredient with efficacy vs. lice the mean range treatment dose is 77.0mg/kg vs. 85.7mg/kg in the study. There is no statistical significance between the values. A second conclusion based on the reviewer comments is the 42 days post treatment value demonstrates that almost half of the dogs had lice. The label claim sought by the registrant is a one month claim not a 42 day claim. At the one month interval the permethrin data shows that seven of the ten dogs evaluated were free of lice (only one dog had count of one), the study authors state that treatment failure did not appear to be from dose related issues. The animals treatment failure by the remaining dogs may have been based on exposure to other dogs infected with lice since the study was an in life field study. Currently EPA has registered products such as Exspot by Pfizer Animal Health the control used for the study at similar levels of permethrin as demonstrated above. The data does support the claim as proposed on the label.

Our Response: The Pesticide Efficacy Review Committee (PERC) considered the comments made by Summit VetPharm, and the reviewer's findings are not altered.

Although the registered SVP7 dose rate is higher than the dose rates tested (see calculations below), there were too few animals in the study.

(1.6 ml) 0.06 fl oz for weights 2.5 to 20 lbs:
for a 20 lb dog, the permethrin application rate is equivalent to 193 mg/kg
(3.6 ml) 0.12 fl oz for weights 20 to 55 lbs:
for a 55 lb dog, the permethrin application rate is equivalent to 158 mg/kg
(4.7 ml) 0.16 fl oz for weights 56 to 95 lbs
for a 95 lb dog, the application rate is equivalent to 119.5 mg/kg
8 ml) 0.3 fl oz for over 95 pounds
for a 120 lb dog, the application rate is equivalent to 153 mg/kg.

At a minimum, the study design must include 24 animals. Mean weight should be toward the upper end of the weight group (e.g, 1.6. ml applied to dogs weighing 15-20 lbs, as opposed to 1.6. ml applied to dogs weighing 2.5 -5 lbs). Raw data must be submitted, and include individual body weights, pre-treatment and post-treatment counts. Since two aduclides are used together, the study should be performed on the exact formulation.

3. Delete all claims relating to mites.

Company Response: Mites. EPA's reviewer states that "This study cannot be used to support a mite claim, since the application rate is not comparable. A review of the calculations, again understanding that the permethrin in the formulation would be responsible for mite efficacy demonstrates that the efficacy levels of permethrin are significantly statistically similar on a mg/kg dose to body weight with 14 of the 19 animals in the conversion table based on current label claims would receive larger doses of permethrin vs. the Exspot .

Ex-Spot vs. (Vectra 3D analysis)SVP7

Weight of dog Kgs..	mg/kg Ex-Spot	mg/kg SVP7
1	650.0	N/A
2	325.0	461.5
3	216.7	307.7
4	162.5	230.8
5	130.0	184.6
6	108.3	153.8
7	92.9	131.9
8	81.3	115.4
9	72.2	102.6
10	65.0	216.5
11	59.1	185.6
12	54.2	162.4
13	50.0	144.3
14	46.4	129.9
15	218.2	118.1
16	200.0	108.3
17	184.6	99.9
18	171.4	92.8
19	160.0	86.6
Average	160.4	168.5

Based on the information provided in the above chart SVP7 has a mean average dose of 168.5 mg/kg vs. a mean average dose of 160.4 mg/kg for Exspot. These values are less than 5% of total dose within the certified limits that could be delivered in real world setting. EPA's conclusion that the rates are not comparable is incorrect and in fact the permethrin dose of SVP7 is greater than the registered approved product. The data does support the proposed label claim.

Our Response: The Pesticide Efficacy Review Committee (PERC) considered the comments made by Summit VetPharm, and the reviewer's findings are not altered. See comments under # 2 above.

4. Delete all claims for flies

Registrant Response: The registrant agrees that the studies evaluated included a spray-on formulation, however, the laboratory did calculate the use rate put on each animal used in the study. Understanding the basic premise of the submission was to confirm the efficacy of a permethrin, pyriproxyfen formulation vs. flies, Summit believes the data does permit the reader to calculate and assess the treatment level for comparison. The basic calculation demonstrates that the product was efficacious at a dose below the use level of SVP7. The registrant in its calculation did not include in its calculation that in some cases the animal the test animal was treated with as much as 80 ml of product, which would have resulted in some minimal runoff which would have further lowered the actual treatment dose. This would not be the case with SVP7.

The imidacloprid permethrin study was submitted to demonstrate the efficacy of a spot-on product containing permethrin at similar but slightly lower dose vs. SVP7. The calculations for the product comparison using the pet spray average dose vs. SVP7 (Vectra 3D) dose is slightly higher on a milligrams per meter squared basis. Mgs/m² was chosen as the measure since (1) it was the unit of measure chosen by the researcher (2) the permethrin is a contact insecticide, therefore it is scientifically justified.

Duowin (spray) vs. Vectra 3D analysis (SVP7)

Weight in kgs.	Duowin permethrin mgs/m ²	Vectra 3D permethrin mgs/m ²
8	1880	1463
7.5	1855	1463
16	2387	3289
10.5	2100	3289
Average	2055.5	2376

The data offered below is based on data published by Bayer in evaluating K9 Advantix formulations. The current registered product contains 44% permethrin vs. the 50% in the test formulation. The data demonstrates that the permethrin dose available from an SVP7 treatment is approximately twice the available rate in the test formulation. Summit and EPA would agree that the ingredients imidacloprid and dinotefuran have not been shown to demonstrate efficacy vs. flies at the concentrations in the formulations; therefore, they would not affect the efficacy i.e., permethrin has been demonstrated to be effective and the concentration of permethrin in SVP7 would be sufficient to support the proposed label claim.

50% permethrin formulation vs. Vectra 3D analysis (SVP7)

Weight in kgs.	50% permethrin	Vectra 3D permethrin
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	mgs/m ²	mgs/m ²
2	666.7	3848.5
3	750.0	2886.4
4	800.0	2309.1
5	862.1	1847.2
6	909.1	1749.3
7	972.2	1603.6
8	1000.0	1443.2
9	1046.5	1342.5
10	1087.0	2823.9
Average	899.3	2002.9
577.28	(dose for Vectra 3D small dog and puppy size)	

Our Response: The Pesticide Efficacy Review Committee (PERC) considered the comments made by Summit VetPharm, and the reviewer's findings are not altered. PERC considered the use of data on a spray product to be unacceptable. The data submitted must reflect the manner in which the product is applied. For a general fly control claim, 3 species of flies must be tested (house fly, one species of biting flies, one species of choice).

5. Delete the sentence "Approximately 95% of the flea population in a household infestation are immature fleas stages that live in the dog's environment."

Registrant Response: The statement "approximately 95% of the flea population in a household..." is not meant to be a claim but a scientific fact understood and taught to veterinarians. The appearance of the statement on the label was to familiarize the EPA with this parasitology fact so that the registrant could quote this information in documents prepared for veterinary use emphasizing the importance of an Insect Growth Regulator (IGR) in the control of fleas in the household. The registrant proposes the following statements as alternatives; "Approximately 95% of the flea population in a household infestation are immature flea stages, SVP7 contains pyriproxyfen an insect growth regulator for control of immature flea stages" "Immature flea stages are a major component of flea infestations, SVP7 contains pyriproxyfen which controls flea eggs, larvae and pupae."

Our Response: The PERC considered the alternate language, and will allow: "Immature flea stages are a major component of flea infestations, SVP7 contains pyriproxyfen which controls flea eggs, larvae and pupae."

6. Delete reference to the phrase "that may transmit disease".

Registrant Response: Delete "that may transmit disease" use of this statement was approved on prior labeling following EPA request that we insert "may" in the phrase. Could EPA advise why statement is no longer acceptable?

Our Response: The term "disease" is too broad.

7. Specify "Sold only by veterinarians" (no parentheses).

Registrant Response: The product is sold exclusively to veterinarians, by the choice of the registrant. The registrant believes that the implications of removing the parenthesis could result in the product appearing to be classified as a restricted use product. The product does not meet the criteria of restricted use and the registrant should not be limited by this marketing restriction. The registrant maintains a track and trace system which allows it to track product from manufacture through distribution and ultimately delivery at the hospital and clinic. The current claims of: "Sold (only) by veterinarians" and "(Only) available from licensed veterinarians" should remain as stated.

Our Response: As stated in previous efficacy review, this is a deferral to PM. Use of parentheses infers product to be marketed through vets and over-counter.

8. Delete all references to the term "Clinic". (see note below)

Registrant Response: EPA continues to misinterpret the use of "clinic" and "Hospital". These statements are meant to imply large pack sizes. Consumer packs are typically sold in three or six unit doses. Larger packs would be sold directly to veterinarian for use in the hospital for single treatment use. Veterinarians are often called upon to treat animals flea or tick infested pets in clinics for any number of reasons including boarding requirements, emergency surgery and dose tolerance in some cases clients choose to have the veterinarian administer treatment monthly. The statement is not meant to imply efficacy or medical approval rather it is a packaging size. We request that EPA reconsider the request and comment on: medipack, veterinary pack, summit pack.

Our Response: See item #8 above. This is a deferral to PM.

9. Delete "Veterinarians recommend year round use of an ectoparasite, such as SVP7."; "Veterinarians [and the Companion Animal Parasite Council (CAPC) (often) recommend year round use..", "Monthly treatment is recommended... and "...that your pet needs year round."

Company Response: Delete statements about recommended year round use. The Companion Animal Parasite Council which is primarily composed of veterinarians and veterinary parasitologist - from veterinary schools throughout the United States - continue to discuss this important message stressing the importance of year round parasite control and its importance to the pet and household. Summit believes the claims on the label are constant and not confusing, year round control is important. In response to EPA comment about over-the-counter vs. veterinarian only with regard to this message there is no confusion all pet owners including those choosing OTC remedies should treat year round.

Our Response: Defer to PM. The term "recommend" is unenforceable.

10. Delete reference to the phrase "...may reduce the incidence of FAD."

Company Response: EPA does not appear to be consistent with their request. In one statement Summit is advised to delete a claim of "may reduce the incidence of FAD" and in a second statement Summit is told to revise statement to read "Svp7 kills fleas that may cause flea allergy dermatitis" Summit believes both statements should be permitted.

Our Response: The phrase is unacceptable. The phrases "SVP7 kills fleas that may cause flea allergy dermatitis" and "May reduce the incidence of FAD" have different meanings.

11. Delete reference to claims "kills on contact" and "kills them on contact".

Company Response: SVP7 is a contact insecticide. Information on the active ingredients documents that these active ingredients work by the insect coming in contact with the chemical, ingestion is not required. Since the registrant is seeking to answer an often asked question on how does the product work, we believe this claim is correct and should be permitted.

Our Response: The Pesticide Efficacy Review Committee (PERC) considered the comments made by Summit VetPharm, and the reviewer's findings are not altered. The claims are still objectionable, since the implication is the product works immediately.

Note: The registrant has not objected to the following claims we found objectionable; PM needs to check label to see if these claims were deleted.

- Delete reference to the terms "eliminates" and "eliminating".
- Delete reference to the term "optimal" or "optimum" everywhere it occurs on the label.
- Delete all reference to term "persistent".
- Revise the phrase "at least one month" to read "for up to a month" everywhere it occurs on the labeling.
- Specify "SVP7 contains dinotefuran.....with onset of flea knockdown in less than 2 hours."
- Revi "Repels and kills mosquitoes....and vector for heartworm.." to read "Repels and kills mosquitoes (Culex spp, Ochlerotatus spp, Aedes spp) which may vector heartworm (Dirofilaria immitis) for up to one month.
- Delete the sentence "Kills over 96% of fleas in 6 hours and up to 100% in 12 hours."
- Revise "SVP7 is useful..." to read "SVP7 kills fleas that may cause flea allergy dermatitis (FAD).
- Specify "...which may vector heartworm (Dirofilaria immitis) for a month.
- Specify "Kills fleas that may transmit bartonellosis and tapeworm."
- Delete reference to the term "hospital clinic pack. (see note below)
- Revise "Protects against all Ixodes species" to read "Protect against all types of Ixodes species attacking dogs."

- Revise "Kills the vectors that may cause Lyme disease..." to read "Kills the listed pests that may transmit Lyme disease..."
- Revise "SVP7 destroys the flea infestation.." to read "SVP7 controls the flea infestation..."
- Delete reference to "the most complete" everywhere it occurs on the label.